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SEARCH REQUEST FORM

Requester's Full Name: Jeffrey E. Russel Examiner #: 62785 Date: 5-13-2005
Art Unit: 1654 Phone Number: 2-0769 Serial Number: 10/666,095
Location (Bldg/Room#): REN 3D19 (Mailbox #): REN 3C18 Results Format Preferred (circle): PAPER DISK

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To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Anti-Fibril Peptides

Inventors (please provide full names): R. Hammer, Y. Fu, J. Arcain, T. Miller, M. McLaughlin, R. McCarley

Earliest Priority Date: 9-18-2003

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search SEQ ID NO: 6 (KXVXFXK) in STN, in the U.S. patent appl. sequence database (pending, published, & issued), and in Geneseq/Uniprot/PIR.

Thank you.

JER

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Type of Search

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_____ AA Sequence (#)
_____ Structure (#)
_____ Bibliographic
_____ Litigation
_____ Fulltext
_____ Other

Vendors and cost where applicable

_____ STN _____ Dialog
_____ Questel/Orbit _____ Lexis/Nexis
_____ Westlaw _____ WWW/Internet
____ In-house sequence systems
__ Commercial ___ Oligomer ___ Score/Length
__ Interference ___ SPDI ___ Encode/Transl
_____ Other (specify)

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L1        11074 SEA FILE=REGISTRY ABB=ON  PLU=ON  K.V.F.K|KXVXFXK/SQSP
L2          124 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND SQL=<50
L3           94 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2
L4           62 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND PD=<SEPTEMBER 18, 2003

L5          242 SEA FILE=REGISTRY ABB=ON  PLU=ON  FIBRIL?
L6        97474 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 OR FIBRIL?
L7        97701 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 OR ANTIFIBRIL?
L8            9 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND L7


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L8   ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:860419  HCAPLUS Full-text
DOCUMENT NUMBER:          140:174980
TITLE:                    The peptide KLVFF-K6 promotes β-amyloid(1-40)
                          protofibril growth by association but does not alter
                          protofibril effects on cellular reduction of
                          3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium
                          bromide (MTT)
AUTHOR(S):                Moss, Melissa A.; Nichols, Michael R.; Reed, Dana Kim;
                          Hoh, Jan H.; Rosenberry, Terrone L.
CORPORATE SOURCE:         Department of Neurosciences, Mayo Clinic,
                          Jacksonville, FL, USA
SOURCE:                   Molecular Pharmacology (2003), 64(5),
                          1160-1168
```

CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The peptide KLVFF-K6 was observed to simultaneously enhance amyloid β-protein (Aβ) **fibrillogenesis** and decrease cellular toxicity, as measured in a 3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide (MTT) reduction assay. It was postulated that accelerated Aβ aggregation and precipitation induced by KLVFF-K6 may lead to an increase in less toxic insol. **fibrils** at the expense of more toxic soluble protofibrils. In a previous study, we distinguished between two modes of protofibril growth:. Elongation by monomer deposition and. Direct protofibril-protofibril association These growth mechanisms could be resolved by varying Aβ monomer and NaCl concns. Using assays designed to isolate these distinct modes of protofibril growth, we report here that larger Aβ aggregates formed in the presence of KLVFF-K6 resulted from enhanced protofibril association 3H-Radiomethylated KLVFF-K6 bound to associated protofibrils with an apparent K6 of 180 nM, and concns. of free [3H]KLVFF-K6 in this range were sufficient to convert soluble protofibrils to sedimentable **fibrils**. However, promotion of Aβ protofibril association by KLVFF-K6 had no effect on Aβ-induced decreases in cellular MTT reduction Therefore, our data do not support the proposal that insol. **fibrils** formed with KLVFF-K6 are less toxic than soluble protofibrils. KLVFF-K6 did not alter rates of protofibril elongation by monomer deposition. In contrast, when added to Aβ monomers isolated with the use of size-exclusion chromatog., KLVFF-K6 inhibited **fibrillogenesis**, as measured by thioflavin T fluorescence, and this inhibition was paralleled by a failure to alter cellular MTT reduction

IT **224645-08-3**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide KLVFF-K6 promotes β-amyloid(1-40) protofibril growth by association but does not alter protofibril effects on cellular reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT))

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:811319 HCAPLUS Full-text
DOCUMENT NUMBER: 139:321569
TITLE: Targeted Control of Kinetics of β-Amyloid Self-association by Surface Tension-modifying Peptides
AUTHOR(S): Kim, Jin Ryoun; Gibson, Todd J.; Murphy, Regina M.
CORPORATE SOURCE: Department of Chemical Engineering, University of Wisconsin-Madison, Madison, WI, 53706, USA
SOURCE: Journal of Biological Chemistry (2003), 278(42), 40730-40735
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Brain tissue from Alzheimer's patients contains extracellular senile plaques composed primarily of deposits of **fibrillar** aggregates of β-amyloid peptide. β-Amyloid aggregation is postulated to be a major factor in the onset of this neurodegenerative disease. Recently proposed is the hypothesis that oligomeric intermediates, rather than fully formed insol. **fibrils**, are cytotoxic. Previously, the authors reported the discovery of peptides that accelerate β-amyloid aggregation yet inhibit toxicity in vitro, in support of

this hypothesis. These peptides contain two domains: a recognition element designed to bind to β-amyloid and a disrupting element that alters β-amyloid aggregation kinetics. Here the authors show that the aggregation rate-enhancing activity of the disrupting element correlates strongly with its ability to increase surface tension of aqueous solns. Using the Hofmeister series as a guide, the authors designed a novel peptide with terminal side-chain trimethylammonium groups in the disrupting domain. The derivatized peptide greatly increased solvent surface tension and accelerated β-amyloid aggregation kinetics by severalfold. Equivalent increases in surface tension in the absence of a recognition domain had no effect on β-amyloid aggregation. These results suggest a novel strategy for targeting localized changes in interfacial energy to specific proteins, as a way to selectively alter protein folding, stability, and aggregation.

IT **354801-68-6**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(targeted control of kinetics of β-amyloid self-association by surface tension-modifying peptides)

IT **224645-08-3P 614751-68-7P**
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(targeted control of kinetics of β-amyloid self-association by surface tension-modifying peptides)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:478355 HCAPLUS Full-text
DOCUMENT NUMBER: 139:147846
TITLE: Specific Compositions of Amyloid-β Peptides as the Determinant of Toxic β-Aggregation
AUTHOR(S): Yoshiike, Yuji; Chui, De-Hua; Akagi, Takumi; Tanaka, Nobuo; Takashima, Akihiko
CORPORATE SOURCE: Laboratory for Alzheimer's Disease, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako-shi, Saitama, 351-0198, Japan
SOURCE: Journal of Biological Chemistry (2003), 278(26), 23648-23655
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Alzheimer's disease (AD) may be caused by toxic aggregates formed from amyloid-β (Aβ) peptides. By using Thioflavin T, a dye that specifically binds to β-sheet structures, the authors found that highly toxic forms of Aβ-aggregates were formed at the initial stage of fibrillogenesis, which is consistent with recent reports on Aβ oligomers. Formation of such aggregates depends on factors that affect both nucleation and elongation. As reported previously, addition of Aβ42 systematically accelerated the nucleation of Aβ40, most likely because of the extra hydrophobic residues at the C terminus of Aβ42. At Aβ42-increased specific ratio (Aβ40:Aβ42 = 10:1), not only accelerated nucleation but also induced elongation were observed, suggesting pathogenesis of early-onset AD. Because a larger proportion of Aβ40 than Aβ42 was still required for this phenomenon, the authors assumed that elongation does not depend only on hydrophobic interactions. Without any change in the C-terminal hydrophobic nature, elongation was effectively induced by mixing wild type Aβ40 with Italian variant Aβ40 (E22K) or Dutch variant (E22Q). The

authors suggest that Aβ peptides in specific compns. that balance hydrophilic and hydrophobic interactions promote the formation of toxic β-aggregates. These results may introduce a new therapeutic approach through the disruption of this balance.

IT 302905-01-7
RL: BSU (Biological study, unclassified); BIOL (Biological study) (specific compns. of amyloid-β peptides as determinant of toxic β-aggregation)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:173628 HCAPLUS Full-text
DOCUMENT NUMBER: 138:215336
TITLE: Application of peptide conjugates in diagnosis and treatment of Alzheimer's disease
INVENTOR(S): Stein, Stanley
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003018609	A2	20030306	WO 2002-US26889	20020823 <--
WO 2003018609	A3	20031016		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-314382P P 20010823

AB A chemical compound and a method for its use in the diagnosis and treatment of Alzheimer's disease in which the at least the sequence of the D-isomers of the amino acids (phenylalanine-phenylalanine-valine-leucine-lysine) is capable of crossing the blood brain barrier, recognizing the formation of plaques characteristic of the pathogenesis of Alzheimer's disease, and interfering with the formation of fibril from beta amyloid peptide effecting an inhibition of the disease process.

IT 500369-44-8DP, reaction product with Orn6Gly5 500369-44-8P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation) (application of peptide conjugates in diagnosis and treatment of Alzheimer's disease)

IT 500369-57-3
RL: RCT (Reactant); RACT (Reactant or reagent) (application of peptide conjugates in diagnosis and treatment of Alzheimer's disease)

L8 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:716949 HCAPLUS Full-text
DOCUMENT NUMBER: 136:65807

TITLE: Identification and Characterization of Key Kinetic Intermediates in Amyloid β-protein **Fibrillogenesis**

AUTHOR(S): Kirkitadze, Marina D.; Condron, Margaret M.; Teplow, David B.

CORPORATE SOURCE: Center for Neurologic Diseases and Department of Neurology (Neuroscience), Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Journal of Molecular Biology (2001), 312(5), 1103-1119
CODEN: JMOBAK; ISSN: 0022-2836

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Amyloid β-protein (Aβ) assembly into toxic oligomeric and **fibrillar** structures is a seminal event in Alzheimer's disease, therefore blocking this process could have significant therapeutic benefit. A rigorous mechanistic understanding of Aβ assembly would facilitate the targeting and design of **fibrillogenesis** inhibitors. Prior studies have shown that Aβ **fibrillogenesis** involves conformational changes leading to the formation of extended β-sheets and that an α-helix-containing intermediate may be involved. However, the significance of this intermediate has been a matter of debate. We report here that the formation of an oligomeric, α-helix-containing assembly is a key step in Aβ **fibrillogenesis**. The generality of this phenomenon was supported by conformational studies of 18 different Aβ peptides, including wild-type Aβ(1-40) and Aβ(1-42), biol. relevant truncated and chemical modified Aβ peptides, and Aβ peptides causing familial forms of cerebral amyloid angiopathy. Without exception, **fibrillogenesis** of these peptides involved an oligomeric α-helix-containing intermediate and the kinetics of formation of the intermediate and of **fibrils** was temporally correlated. The kinetics varied depending on amino acid sequence and the extent of peptide N- and C-terminal truncation. The pH dependence of helix formation suggested that Asp and His exerted significant control over this process and over **fibrillogenesis** in general. Consistent with this idea, Aβ peptides containing Asp → Asn or His → Gln substitutions showed altered **fibrillogenesis** kinetics. These data emphasize the importance of the dynamic interplay between Aβ monomer conformation and oligomerization state in controlling **fibrillogenesis** kinetics. (c) 2001 Academic Press.

IT 383200-59-7 383200-60-0
RL: BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); PROC (Process)
(model peptide; identification and characterization of key kinetic intermediates in amyloid β-protein **fibrillogenesis**)

REFERENCE COUNT: 110 THERE ARE 110 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:408725 HCAPLUS Full-text

DOCUMENT NUMBER: 135:174666

TITLE: Structure-Function Relationships for Inhibitors of β-Amyloid Toxicity Containing the Recognition Sequence KLVFF

AUTHOR(S): Lowe, Tao L.; Strzelec, Andrea; Kiessling, Laura L.; Murphy, Regina M.

CORPORATE SOURCE: Departments of Chemical Engineering and Chemistry, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Biochemistry (2001), 40(26), 7882-7889
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB β-Amyloid (Aβ), the primary protein component of Alzheimer's plaques, is neurotoxic when aggregated into fibrils. We have devised a modular strategy for generating compds. that inhibit Aβ toxicity. These compds. contain a recognition element, designed to bind to Aβ, linked to a disrupting element, designed to interfere with Aβ aggregation. On the basis of this strategy, a hybrid peptide was synthesized with the sequence KLVFF (residues 16-20 of Aβ) as the recognition element and a lysine hexamer as the disrupting element; this compound protects cells in vitro from Aβ toxicity [Pallitto, M. M., et al. (1999) Biochem. 38, 3570]. To determine if the length of the disrupting element could be reduced, peptides were synthesized that contained the KLVFF recognition element and a sequence of one to six lysines as disrupting elements. All compds. enhanced the rate of aggregation of Aβ, with the magnitude of the effect increasing as the number of lysines in the disrupting element increased. The greatest level of protection against Aβ toxicity was achieved with compds. containing disrupting elements of three or more lysines in sequence. A peptide with an anionic disrupting element, KLVFFEEEE, had activity similar to that of KLVFFKKKK, in both cellular toxicity and biophys. assays, whereas a peptide with a neutral polar disrupting element, KLVFFSSSS, was ineffective. Protective compds. retained activity even at an inhibitor:Aβ molar ratio of 1:100, making these some of the most effective inhibitors of Aβ toxicity reported to date. These results provide critical insight needed to design more potent inhibitors of Aβ toxicity and to elucidate their mechanism of action.

IT **354801-65-3 354801-66-4 354801-68-6 354801-69-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-function relationships for inhibitors of β-amyloid toxicity containing recognition sequence KLVFF)

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:754711 HCAPLUS Full-text
DOCUMENT NUMBER: 133:318297
TITLE: Sequence-determined DNA fragments and corresponding encoded polypeptides from corn and Arabidopsis
INVENTOR(S): Alexandrov, Nickolai; Brover, Vyacheslav; Chen, Xianfeng; Subramanian, Gopalakrishnan; Troukhan, Maxim E.; Zheng, Liansheng; Dumas, J.
PATENT ASSIGNEE(S): Ceres Inc., USA
SOURCE: Eur. Pat. Appl., 339 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 16
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

EP 1033405	A2	20000906	EP 2000-301439		20000225 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
CA 2300692	AA	20000825	CA 2000-2300692		20000225 <--
CA 2302828	AA	20001006	CA 2000-2302828		20000406 <--
EP 1055728	A2	20001129	EP 2000-303770		20000504 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
EP 1054060	A2	20001122	EP 2000-304161		20000517 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					

PRIORITY APPLN. INFO.:	US 1999-121825P	P	19990225
	US 1999-145918P	P	19990727
	US 1999-145951P	P	19990728
	US 1999-146386P	P	19990802
	US 1999-146388P	P	19990802
	US 1999-146389P	P	19990802
	US 1999-147038P	P	19990803
	US 1999-147204P	P	19990804
	US 1999-147302P	P	19990804
	US 1999-147192P	P	19990805
	US 1999-147260P	P	19990805
	US 1999-147303P	P	19990806
	US 1999-147416P	P	19990806
	US 1999-147493P	P	19990809
	US 1999-147935P	P	19990809
	US 1999-148171P	P	19990810
	US 1999-148319P	P	19990811
	US 1999-148341P	P	19990812
	US 1999-148565P	P	19990813
	US 1999-148684P	P	19990813
	US 1999-123180P	P	19990305
	US 1999-123548P	P	19990309
	US 1999-125788P	P	19990323
	US 1999-126264P	P	19990325
	US 1999-126785P	P	19990329
	US 1999-127462P	P	19990401
	US 1999-128234P	P	19990406
	US 1999-128714P	P	19990408
	US 1999-129845P	P	19990416
	US 1999-130077P	P	19990419
	US 1999-130449P	P	19990421
	US 1999-130510P	P	19990423
	US 1999-130891P	P	19990423
	US 1999-131449P	P	19990428
	US 1999-132048P	P	19990430
	US 1999-132407P	P	19990430
	US 1999-132484P	P	19990504
	US 1999-132485P	P	19990505
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	US 1999-132487P	P	19990506
	US 1999-132863P	P	19990507
	US 1999-134256P	P	19990511
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	US 1999-134221P	P	19990514
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US	1999-135353P	P	19990521
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US	1999-136782P	P	19990528
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US	1999-137528P	P	19990603
US	1999-137502P	P	19990604
US	1999-137724P	P	19990607
US	1999-138094P	P	19990608

AB The present invention provides DNA mols. that constitute fragments of the genome and cDNAs from Zea mays mays (HYBRID SEED #35A19) and Arabidopsis thaliana (ecotype Wassilewski), and polypeptides encoded thereby. The DNA mols. are useful for specifying a gene product in cells, either as a promoter or as a protein coding sequence or as an UTR or as a 3' termination sequence, and are also useful in controlling the behavior of a gene in the chromosome, in controlling the expression of a gene or as tools for genetic mapping, recognizing or isolating identical or related DNA fragments, or identification of a particular individual organism, or for clustering of a group of organisms with a common trait. Arabidopsis DNA is used in the present experiment, but the procedure is a general one. Protocols are provided for Southern hybridizations and transformation of carrot cells. [This abstract record is one of 15 records supplemental to CA13316218528Q necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT **253847-42-6 302654-48-4.302920-12-3**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; sequence-determined DNA fragments and corresponding encoded polypeptides from corn and Arabidopsis)

L8 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2000:641916 HCAPLUS Full-text
DOCUMENT NUMBER:	133:320545
TITLE:	Substitutions at codon 22 of Alzheimer's Aβ peptide induce diverse conformational changes and apoptotic effects in human cerebral endothelial cells
AUTHOR(S):	Miravalle, Leticia; Tokuda, Takahiko; Chiarle, Roberto; Giaccone, Giorgio; Bugiani, Orso; Tagliavini, Fabrizio; Frangione, Blas; Ghiso, Jorge
CORPORATE SOURCE:	Department of Pathology, New York University School of Medicine, New York, NY, 10016, USA
SOURCE:	Journal of Biological Chemistry (2000), 275(35), 27110-27116 CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER:	American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Cerebral amyloid angiopathy is commonly associated with normal aging and Alzheimer's disease and it is also the principal feature of hereditary cerebral hemorrhage with amyloidosis Dutch type, a familial condition associated to a point mutation G to C at codon 693 of the amyloid β (Aβ) precursor protein gene resulting in a Glu to Gln substitution at position 22 of the Aβ (E22Q). The patients carrying the AβE22Q variant usually present with lobar cerebral hemorrhages before 50 yr of age. A different mutation described in several members of three Italian kindred who presented with recurrent hemorrhagic strokes late in life, between 60 and 70 yr of age, also

associated with extensive cerebrovascular amyloid deposition has been found at the same position 22, this time resulting in a Glu to Lys substitution (E22K). The authors have compared the secondary structure, aggregation, and **fibrillization** properties of the two Aβ40 variants and the wild type peptide. Using flow cytometry anal. after staining with propidium iodide and annexin V, the authors also evaluated the cytotoxic effects of the peptides on human cerebral endothelial cells in culture. Under the conditions tested, the E22Q peptide exhibited the highest content of β-sheet conformation and the fastest aggregation/**fibrillization** properties. The Dutch variant also induced apoptosis of cerebral endothelial cells at a concentration of 25 μM, whereas the wild type Aβ and the E22K mutant had no effect. The data suggest that different amino acids at position 22 confer distinct structural properties to the peptides that appear to influence the onset and aggressiveness of the disease rather than the phenotype.

IT **302905-01-7**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(substitutions at codon 22 of Alzheimer's Aβ peptide induce diverse conformational changes and apoptotic effects in human cerebral endothelial cells in relation to cerebral amyloid angiopathy)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:148185 HCAPLUS Full-text
DOCUMENT NUMBER: 130:347290
TITLE: Recognition sequence design for peptidyl modulators of β-amyloid aggregation and toxicity
AUTHOR(S): Pallitto, Monica M.; Ghanta, Jyothi; Heinzelman, Peter; Kiessling, Laura L.; Murphy, Regina M.
CORPORATE SOURCE: Departments of Chemical Engineering and Chemistry, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Biochemistry (1999), 38(12), 3570-3578
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB β-Amyloid (Aβ), the primary protein component of Alzheimer's plaques, is neurotoxic when aggregated into **fibrils**. We have devised a modular strategy for generating compds. that inhibit Aβ toxicity, based on linking a recognition element for Aβ to a disrupting element designed to interfere with Aβ aggregation. One such compound, with the 15-25 sequence of Aβ as the recognition element and a lysine hexamer as the disrupting element, altered Aβ aggregation kinetics and protected cells from Aβ toxicity [Ghanta et al. (1996) J. Biol. Chemical 271, 29525]. To optimize the recognition element, peptides of 4-8 residues composed of overlapping sequences within the 15-25 domain were synthesized, along with hybrid compds. containing those recognition sequences coupled to a lysine hexamer. None of the recognition peptides altered Aβ aggregation kinetics and only two, KLVFF and KLVF, had any protective effect against Aβ toxicity. The hybrid peptide KLVFF-KKKKKK dramatically altered Aβ aggregation kinetics and aggregate morphol. and provided significantly improved protection against Aβ toxicity compared to the recognition peptide alone. In contrast, FAEDVG-KKKKKK possessed only modest inhibitory activity and had no marked effect on Aβ aggregation. The scrambled sequence VLFKF was nearly as effective a recognition domain as KLVFF, suggesting the hydrophobic characteristics of the recognition sequence are

critical None of the cytoprotective peptides prevented Aβ aggregation; rather, they increased aggregate size and altered aggregate morphol. These results suggest that coupling recognition with disrupting elements is an effective generalizable strategy for the creation of Aβ inhibitors. Significantly, prevention of Aβ aggregation may not be required for prevention of toxicity.

IT 224645-08-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(recognition sequence design for peptidyl modulators of β-amyloid aggregation and toxicity)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> select rn 18 1-9
E# OR SYSTEM LIMIT REACHED WHILE PROCESSING ANSWER 7
E1 THROUGH E999 ASSIGNED

=> del select
DELETE ALL E# DEFINITIONS? (Y)/N:y

=> select hit rn 18 1-9
E1 THROUGH E14 ASSIGNED

=> fil reg
FILE 'REGISTRY' ENTERED AT 12:26:22 ON 20 MAY 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 19 MAY 2005 HIGHEST RN 850784-62-2
DICTIONARY FILE UPDATES: 19 MAY 2005 HIGHEST RN 850784-62-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:

http://www.cas.org/ONLINE/DBSS/registryss.html

```
=>
=>
=> d his l9-

     (FILE 'HCAPLUS' ENTERED AT 12:25:09 ON 20 MAY 2005)

     FILE 'HCAPLUS' ENTERED AT 12:25:41 ON 20 MAY 2005
               SELECT RN L8 1-9
               DEL SELECT
               SELECT HIT RN L8 1-9

     FILE 'REGISTRY' ENTERED AT 12:26:22 ON 20 MAY 2005
L9            14 S E1-E14
L10           12 S L9 AND L2

=>
=>

=> d .seq l10 1-12

L10  ANSWER 1 OF 12  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   614751-68-7  REGISTRY
CN   L-Lysine, L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-N6-
     [(trimethylammonio)acetyl]-L-lysyl-N6-[(trimethylammonio)acetyl]-L-lysyl-
     N6-[(trimethylammonio)acetyl]-L-lysyl-N6-[(trimethylammonio)acetyl]-L-
     lysyl-N6-[(trimethylammonio)acetyl]-L-lysyl-N6-[(trimethylammonio)acetyl]-
     (9CI)  (CA INDEX NAME)
NTE  modified (modifications unspecified)
SQL  11
RN   614751-68-7  REGISTRY
SQL  11

SEQ      1 KLVFFKKKKK K
           =======
HITS AT:   1-7

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  139:321569

L10  ANSWER 2 OF 12  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   500369-57-3  REGISTRY
CN   L-Phenylalanine, L-lysyl-L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-, polymer
     with α-(carboxymethyl)-ω-(carboxymethoxy)poly(oxy-1,2-
     ethanediyl) (9CI)  (CA INDEX NAME)
NTE  homopolymer
     modified (modifications unspecified)
-------------------------------------------------------------------
 type            ------ location ------         description
-------------------------------------------------------------------
modification        -            -         undetermined modification
-------------------------------------------------------------------
SQL  6
RN   500369-57-3  REGISTRY
SQL  6

SEQ      1 KKLVFF
           ======
```

HITS AT: 1-2, 2-6

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 138:215336

L10 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 500369-44-8 REGISTRY
CN L-Phenylalanine, N6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl-N6-[(1,1-dimethylethoxy)carbonyl]-L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-, polymer with α-(carboxymethyl)-ω-(carboxymethoxy)poly(oxy-1,2-ethanediyl) (9CI) (CA INDEX NAME)
NTE homopolymer
modified (modifications unspecified)

type	------ location ------		description
modification	-	-	undetermined modification
modification	Lys-1	-	(1,1-dimethylethoxy) carbonyl<Boc>
modification	Lys-2	-	(1,1-dimethylethoxy) carbonyl<Boc>

SQL 6
RN 500369-44-8 REGISTRY
SQL 6

SEQ 1 KKLVFF
======
HITS AT: 1-2, 2-6

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 138:215336

L10 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 383200-60-0 REGISTRY
CN L-Valine, L-α-aspartyl-L-alanyl-L-α-glutamyl-L-phenylalanyl-L-arginyl-L-histidyl-L-α-aspartyl-L-serylglycyl-L-tyrosyl-L-α-glutamyl-L-valyl-L-histidyl-L-histidyl-L-glutaminyl-L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-alanyl-L-lysyl-L-α-aspartyl-L-valylglycyl-L-seryl-L-asparaginyl-L-lysylglycyl-L-alanyl-L-isoleucyl-L-isoleucylglycyl-L-leucyl-L-methionyl-L-valylglycylglycyl-L-valyl- (9CI) (CA INDEX NAME)
SQL 40
RN 383200-60-0 REGISTRY
SQL 40

SEQ 1 DAEFRHDSGY EVHHQKLVFF AKDVGSNKGA IIGLMVGGVV
===== ==
HITS AT: 16-22

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 136:65807

L10 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 383200-59-7 REGISTRY
CN L-Alanine, L-α-aspartyl-L-alanyl-L-α-glutamyl-L-phenylalanyl-L-arginyl-L-histidyl-L-α-aspartyl-L-serylglycyl-L-tyrosyl-L-α-glutamyl-L-valyl-L-histidyl-L-histidyl-L-glutaminyl-L-lysyl-L-leucyl-L-

valyl-L-phenylalanyl-L-phenylalanyl-L-alanyl-L-lysyl-L-α-aspartyl-L-valylglycyl-L-seryl-L-asparaginyl-L-lysylglycyl-L-alanyl-L-isoleucyl-L-isoleucylglycyl-L-leucyl-L-methionyl-L-valylglycylglycyl-L-valyl-L-valyl-L-isoleucyl- (9CI) (CA INDEX NAME)
SQL 42
RN 383200-59-7 REGISTRY
SQL 42

SEQ 1 DAEFRHDSGY EVHHQKLVFF AKDVGSNKGA IIGLMVGGVV IA
=====
HITS AT: 16-22

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 136:65807

L10 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 354801-69-7 REGISTRY
CN L-Lysine, L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl- (9CI) (CA INDEX NAME)
SQL 10
RN 354801-69-7 REGISTRY
SQL 10

SEQ 1 KLVFFKKKKK
=======
HITS AT: 1-7

REFERENCE 1: 135:174666

L10 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 354801-68-6 REGISTRY
CN L-Lysine, L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-lysyl-L-lysyl-L-lysyl- (9CI) (CA INDEX NAME)
SQL 9
RN 354801-68-6 REGISTRY
SQL 9

SEQ 1 KLVFFKKKK
=======
HITS AT: 1-7

REFERENCE 1: 139:321569

REFERENCE 2: 137:167565

REFERENCE 3: 135:174666

L10 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 354801-66-4 REGISTRY
CN L-Lysine, L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-lysyl-L-lysyl- (9CI) (CA INDEX NAME)
SQL 8
RN 354801-66-4 REGISTRY
SQL 8

SEQ 1 KLVFFKKK
=======
HITS AT: 1-7

REFERENCE 1: 135:174666

L10 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 354801-65-3 REGISTRY
CN L-Lysine, L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-lysyl- (9CI) (CA INDEX NAME)
SQL 7
RN 354801-65-3 REGISTRY
SQL 7

SEQ 1 KLVFFKK
=======
HITS AT: 1-7

REFERENCE 1: 137:167565

REFERENCE 2: 135:174666

L10 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 302920-12-3 REGISTRY
CN Protein (Arabidopsis thaliana clone Ceres_2139427) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 535: PN: EP1033405 SEQID: 60535 claimed protein
SQL 47
RN 302920-12-3 REGISTRY
SQL 47

SEQ 1 GSFTSTGLVV SSKLPRFSDQ YTLTIDSADP QSISAGKSVQ FTKSVTQ
==== ===
HITS AT: 37-43

REFERENCE 1: 133:318297

L10 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2005 ACS on STN
RN 302905-01-7 REGISTRY
CN L-Valine, L-α-aspartyl-L-alanyl-L-α-glutamyl-L-phenylalanyl-L-arginyl-L-histidyl-L-α-aspartyl-L-serylglycyl-L-tyrosyl-L-α-glutamyl-L-valyl-L-histidyl-L-histidyl-L-glutaminyl-L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-alanyl-L-lysyl-L-α-aspartyl-L-valylglycyl-L-seryl-L-asparaginyl-L-lysylglycyl-L-alanyl-L-isoleucyl-L-isoleucylglycyl-L-leucyl-L-methionyl-L-valylglycylglycyl-L-valyl- (9CI) (CA INDEX NAME)
SQL 40
RN 302905-01-7 REGISTRY
SQL 40

SEQ 1 DAEFRHDSGY EVHHQKLVFF AKDVGSNKGA IIGLMVGGVV
===== ==
HITS AT: 16-22

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 142:371844

REFERENCE 2: 139:147846

REFERENCE 3: 139:147845

REFERENCE 4: 133:320545

```
L10  ANSWER 12 OF 12  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   224645-08-3  REGISTRY
CN   L-Lysine, L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-lysyl-L-
     lysyl-L-lysyl-L-lysyl-L-lysyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   8: PN: US6022859 SEQID: 8 claimed sequence
SQL  11
RN   224645-08-3  REGISTRY
SQL  11

SEQ      1 KLVFFKKKKK K
           =======
HITS AT:   1-7

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  141:135862

REFERENCE   2:  140:174980

REFERENCE   3:  139:321569

REFERENCE   4:  137:167565

REFERENCE   5:  132:146648

REFERENCE   6:  130:347290


=> _

=> d stat que l12
L1         11074 SEA FILE=REGISTRY ABB=ON  PLU=ON  K.V.F.K|KXVXFXK/SQSP
L11            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 AND SQL=7
L12            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11


=>
=>

=> => d his l13

     (FILE 'HCAPLUS' ENTERED AT 12:28:38 ON 20 MAY 2005)
L13            1 S L12 NOT L8

=>
=> d ibib abs hitrn l13 1

L13  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2002:452041  HCAPLUS Full-text
DOCUMENT NUMBER:          137:167565
TITLE:                    Affinity-Based Inhibition of β-Amyloid Toxicity
AUTHOR(S):                Cairo, Christopher W.; Strzelec, Andrea; Murphy,
                          Regina M.; Kiessling, Laura L.
CORPORATE SOURCE:         Departments of Chemistry Biochemistry and Chemical
                          Engineering, University of Wisconsin-Madison, Madison,
                          WI, 53706, USA
SOURCE:                   Biochemistry (2002), 41(27), 8620-8629
                          CODEN: BICHAW; ISSN: 0006-2960
```

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Strategies for interfering with protein aggregation are important for elucidating and controlling the pathologies of amyloid diseases. We have previously identified compds. that block the cellular toxicity of the β-amyloid peptide, but the relationship between their ability to inhibit toxicity and their affinity for Aβ is unknown. To elucidate this relationship, we have developed an assay capable of measuring the affinities of small mols. for β-amyloid peptide. Our approach employs immobilized β-amyloid peptide at low d. to minimize the problems that arise from variability in the β-amyloid aggregation state. We found that low-mol. weight (MW of 700-1700) ligands for β-amyloid can be identified readily by using surface plasmon resonance. The best of these bound effectively (Kd .apprx. 40 μM) to β-amyloid. The affinities measured for peptides in the SPR assay correspond to results from Aβ cell toxicity assays. The most potent ligands for immobilized β-amyloid are the most potent inhibitors of the neuronal cell toxicity of β-amyloid. Compds. with dissocation consts. above .apprx.100 μM did not show significant activity in the cell toxicity assays. Our data support the hypothesis that ligands exhibiting greater affinity for the β-amyloid peptide are effective at altering its aggregation and inhibiting cell toxicity.

IT 354801-65-3
RL: ANT (Analyte); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(amino acid sequence; affinity-based inhibition of β-amyloid toxicity)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> fil reg
FILE 'REGISTRY' ENTERED AT 12:29:47 ON 20 MAY 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 19 MAY 2005 HIGHEST RN 850784-62-2
DICTIONARY FILE UPDATES: 19 MAY 2005 HIGHEST RN 850784-62-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
=>

=> => d .seq l11 1

L11 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 354801-65-3 REGISTRY
CN L-Lysine, L-lysyl-L-leucyl-L-valyl-L-phenylalanyl-L-phenylalanyl-L-lysyl- (9CI) (CA INDEX NAME)
SQL 7
SQL 7

SEQ 1 KLVFFKK
=======
HITS AT: 1-7

REFERENCE 1: 137:167565

REFERENCE 2: 135:174666

=>